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Integrated Assessment of Diastolic and Systolic Ventricular Function Using Diagnostic Cardiac Magnetic Resonance Catheterization

Validation in Pigs and Application in a Clinical Pilot Study

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OBJECTIVES This study sought to develop and validate a method for the integrated analysis of systolic and diastolic ventricular function.

BACKGROUND An integrated approach to assess ventricular pump function, myocontractility (end-systolic pressure–volume relationship [ESPVR]), and diastolic compliance (end-diastolic pressure–volume relation [EDPVR]) is of high clinical value. Cardiac magnetic resonance (CMR) is well established for measuring global pump function, and catheterization-combined CMR was previously shown to accurately measure ESPVR, but not yet the EDPVR.

METHODS In 8 pigs, the CMR technique was compared with conductance catheter methods (gold standard) for measuring the EDPVR in the left and right ventricle. Measurements were performed at rest and during dobutamine administration. For CMR, the ESPVR was estimated with a single-beat approach by synchronizing invasive ventricular pressures with cine CMR–derived ventricular volumes. The EDPVR was determined during pre-load reduction from additional volume data that were obtained from real-time velocity-encoded CMR pulmonary/aortic blood flow measurements. Pre-load reduction was achieved by transient balloon occlusion of the inferior vena cava. The stiffness coefficient β was calculated by an exponential fit from the EDPVR. After validation in the animal experiments, the EDPVR was assessed in a pilot study of 3 patients with a single ventricle using identical CMR and conductance catheter techniques.

RESULTS Bland-Altman tests showed good agreement between conductance catheter–derived and CMR-derived EDPVR. In both ventricles of the pigs, dobutamine enhanced myocontractility ($p < 0.01$), increased stroke volume ($p < 0.01$), and improved diastolic function. The latter was evidenced by shorter early relaxation ($p < 0.05$), a downward shift of the EDPVR, and a decreased stiffness coefficient β ($p < 0.05$). In contrast, in the patients, early relaxation was inconspicuous but the EDPVR shifted left-upward and the stiffness constant remained unchanged. The observed changes in diastolic function were not significantly different when measured with conductance catheter and CMR.

CONCLUSIONS This novel CMR method provides differential information about diastolic function in conjunction with parameters of systolic contractility and global pump function. (J Am Coll Cardiol Img 2009;2:1271–81) © 2009 by the American College of Cardiology Foundation

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Heart failure is a common cause of mortality and death. In pathophysiology, different forms of systolic and diastolic heart failure can be defined (1–3). In many patients, combined forms of systolic and diastolic dysfunction coexist and are difficult to differentiate. Substantiated knowledge about the predominant form of heart failure is essential for optimizing treatments. Thus, an integrated approach for evaluating systolic contractility in conjunction with diastolic relaxation and compliance would be of high clinical value.

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Recent innovations in imaging provided a variety of new methods for the noninvasive assessment of cardiac function. These methods allow determination of stress–strain relation or inflow profiles of the ventricles, for example. However, many of these parameters are pre-load–dependent and/or afterload-dependent or only reflect regional myocardial function. Therefore, analysis of pressure–volume relations is still regarded as the most reliable way to obtain load independent parameters of contractility and diastolic compliance (1,2).

ABBREVIATIONS AND ACRONYMS

β = stiffness constant

CMR = cardiac magnetic resonance

EDPVR = end-diastolic pressure–volume relation

Emax = slope of the end-systolic pressure–volume relation

Emax,i = slope of the end-systolic pressure–volume relation indexed to 100 mg myocardial muscle mass

ESPVR = end systolic pressure–volume relation

τ = parameter of early diastolic relaxation

VEC = velocity-encoded cine

Advances in fast imaging techniques made diagnostic cardiac magnetic resonance (CMR) catheterization a realistic option (4–8). It was shown to provide accurate estimates of the end-systolic pressure–volume relationship (ESPVR) by combining invasive ventricular pressures with cine CMR derived ventricular volumes. The ESPVR is widely considered the optimal quantification of systolic contractile function (6,8).

In the current study, we propose a novel CMR approach that combines real-time–derived ventricular volumes with invasively measured ventricular pressures for assessment of the end-diastolic pressure–volume relationship (EDPVR). The EDPVR characterizes ventricular chamber stiffness in a relatively load-independent fashion and showed practical importance for the assessment of patients with diastolic dysfunction (1,2,9,10).

The aim of this experimental study was to develop a CMR method for assessment of the EDPVR and to validate this method in the pig right and left ventricle using conductance catheter techniques as a gold standard reference. Subsequently, the applicability of this method in a clinical context was evaluated in a pilot study involving patients with a single ventricle after Fontan operation. In these patients, diastolic dysfunction has been reported by several investigators (11,12).

METHODS AND STUDY DESIGN

Animal experiments. The animal experiments were authorized by the responsible animal care authorities. The validation study was conducted in 8 pigs (31 ± 5 kg). The animals were pre-medicated with 5 mg/kg azaperone and 10 mg/kg ketamine intramuscularly. Anesthesia was maintained with 1.5% isoflurane inhalation. All CMR and conductance catheter measurements were performed at end expiratory breath-hold and during muscle relaxation with 0.01 mg/kg vecuronium bromide intravenously. After completion of measurements, animals were euthanized.

The timeline and brief description of the protocol are shown in Figure 1. Right and left ventricular pressure–volume relations were first assessed by conductance catheter (gold standard). Thereafter, the animals were transferred to the neighboring CMR laboratory. All measurements were performed at rest and repeated during continuous infusion of dobutamine at 10 μg/kg/min with at least a 10-min interval between inotropic stimulation and repeated measurements at rest.

Measured parameters. Parameters of ventricular global, myocontractile, and diastolic function were obtained using conductance catheter and/or CMR techniques.

GLOBAL PUMP FUNCTION (BY CINE CMR). This parameter is composed of ventricular end-diastolic, end-systolic, and stroke volume assessed by cine CMR.

MYOCONTRACTILE FUNCTION (BY CONDUCTANCE AND CMR CATHETERIZATION). The slope of the ESPVR (Emax) was defined as a measure of contractility and was derived from the pressure–volume loops as determined with conductance catheter and CMR techniques. The Emax was indexed to 100 mg myocardial muscle mass (Emax,i).

DIASTOLIC FUNCTION (BY CONDUCTANCE AND CMR CATHETERIZATION). From pressure measurements, we derived τ as a parameter of early diastolic relaxation. The stiffness constant (β) was determined from a set of EDPVR and was defined as a measure of diastolic compliance. The β value was

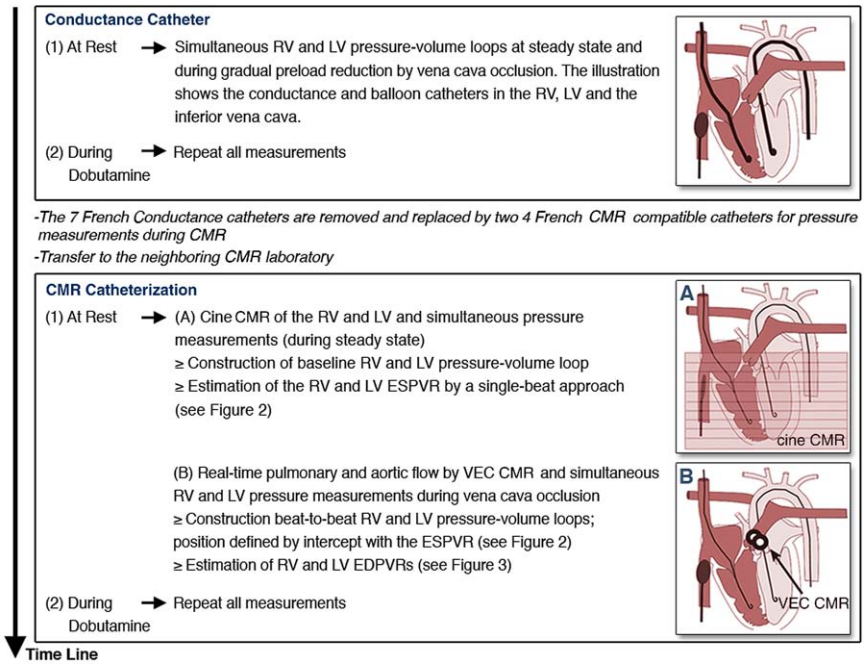

Figure 1. Time Line of the Study

The animals were first assessed at rest and during dobutamine administration using a conductance catheter technique. Then they were moved to the neighboring CMR laboratory and investigated again at rest and during dobutamine application. The figure shows the position of the catheters in the left and right ventricle and the inferior vena cava. The CMR was performed using a cine CMR method in the axial plane (**shaded box in A**) and by VEC CMR measurements in the aorta and the pulmonary truncus (**arrow in B**). CMR = cardiac magnetic resonance; EDPVR = end-diastolic pressure–volume relation; ESPVR = end-systolic pressure–volume relation; LV = left ventricle; RV = right ventricle; VEC = velocity-encoded cine.

calculated from the EDPVR with an exponential regression: $EDP = Ae^{\beta \cdot EDV}$ where EDP = end-diastolic pressure, EDV = end-diastolic volume, and A = curve-fitting constant. The β value was indexed to ventricular volumes for creating a dimensionless index where appropriate.

Concept of CMR-derived EDPVR. Because of its inherent nonlinearity, the assessment of the EDPVR ideally requires pressure–volume data acquired at multiple loading conditions. Therefore, ventricular loading was gradually altered by vena cava balloon occlusion. Beat-to-beat alteration in volume load and pressure were measured simultaneously with real-time CMR and liquid-filled catheters. The concept for measuring EDPVR using CMR-catheterization is based on working steps that are shown in Figures 2 to 4.

STEP A: CINE CMR. Biventricular phasic absolute volumes were acquired over several cardiac cycles with multislice-multiphase cine CMR. During CMR, ventricular pressures were measured continuously, averaged, and synchronized with the cine CMR derived volumes to construct a baseline pressure–volume loop under steady-state conditions. Synchronization of pressures and volumes was achieved by a trigger signal (Fig. 2, left). The ESPVR was estimated from the baseline loop using a single-beat approach as previously described (7,13).

STEP B: REAL-TIME CMR. Instantaneous blood flows were measured using real-time velocity-encoded cine (VEC) CMR in the pulmonary trunk and ascending aorta. Recording of ventricular pressures was started with the beginning of CMR and synchronized with the flow using the trigger signal. At steady state and in the absence of atrioventricular valve insufficiency, effective right or left ventricular stroke volumes are considered being equivalent to the effective antegrade pulmonary or aortic blood flow volumes. Therefore, ventricular chamber volumes can be computed by subtracting the effective stroke volumes from the end-diastolic volume of the cine CMR measurements (marked baseline EDPV in Fig. 3). After 3 to 4 heartbeats, pre-load was lowered by transient balloon occlusion of the vena cava. Importantly, for these unloaded beats

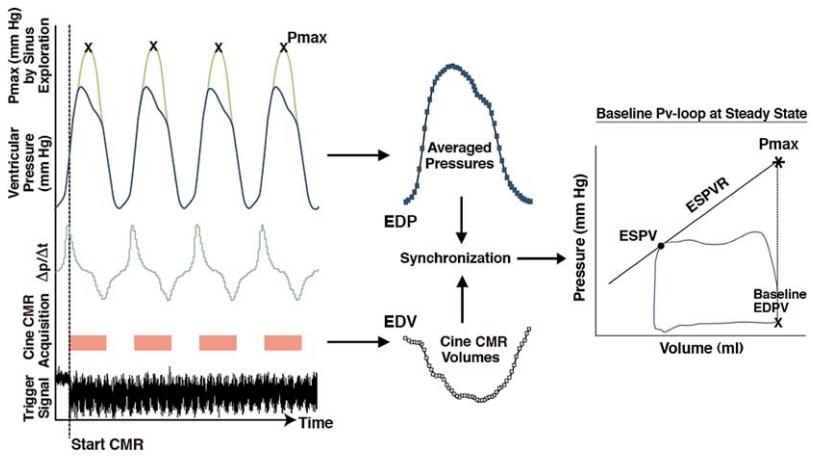

Figure 2. Baseline Pressure–Volume Loop at Steady-State Condition

The baseline loop **(right)** was constructed by synchronizing ventricular pressures with cine CMR–derived absolute volume data. The ESPVR was estimated from a single-beat approach. Pmax was calculated by a sinus wave extrapolation of the ventricular pressure curve. Further details are provided in the text. EDP = end-diastolic pressure; EDPV = end-diastolic pressure–volume point; EDV = end-diastolic volume; ESPV = end-systolic pressure–volume point; Pmax = maximum isovolumic ventricular pressure; Pv = pressure-volume; other abbreviations as in Figure 1.

ventricular filling is unknown, thus the absolute volume (horizontal position of the pressure–volume loop) is undetermined. Initially, end-diastolic volumes of all unloaded loops were arbitrarily arranged to show diminishment in stroke volume.

STEP C: POST-PROCESSING. To calibrate the absolute volume of the flow-derived real-time pressure–volume loops, we matched the end-systolic volume of each unloaded beat with the ESPVR volume intercept at the measured corresponding end-systolic pressure. The resulting end-diastolic pressure–volume points were used to determine the EDPVR and to calculate β.

Conductance catheter. The conductance catheter study was performed using a Leycom signal processor (CD-Leycom, Zoetermeer, the Netherlands) and 6-F to 7-F dual-field catheters (Millar, Houston, Texas). Catheter tips were positioned in the left or right ventricular apex, and measurements were performed during transient pre-load reduction by vena cava balloon occlusion using a 36-mm sizing balloon inflated with isotonic saline solution (AGA Medical, Plymouth, Minnesota). Parallel conductance was determined by the saline dilution method (14). The calibration factor alpha was calculated from CMR-derived stroke volumes.

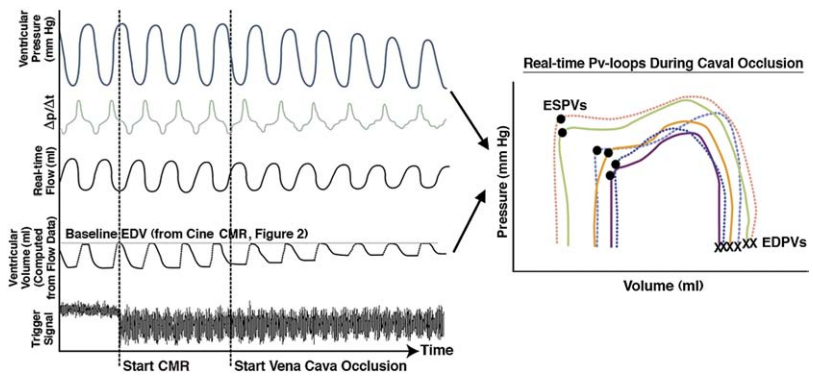

Figure 3. Composition of the Real-Time Pressure–Volume Loops From Simultaneously Measured Ventricular Pressure and Real-Time Velocity-Encoded Cine CMR–Derived Volume Data

Note that initially, end-diastolic volumes of all loops are unknown and were arbitrarily drawn equally spaced to better show the gradual decrease in end-diastolic pressure during unloading. Abbreviations as in Figures 1 and 2.

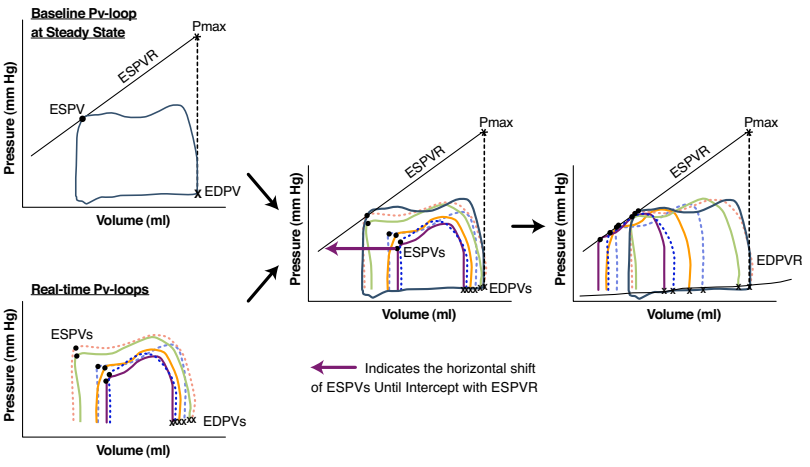

Figure 4. Stepwise Arrangement of Baseline and Real-Time Pressure-Volume Loops for Assessment of EDPVR

The horizontal position of the real-time pressure–volume loops (**lower left** and Fig. 3) was calibrated by matching the end-systolic pressure–volume points with the ESPVR determined from the baseline pressure–volume loop (**upper left** and Fig. 2). The ESPVs of each beat were shifted to match to the intercept of the ESPVR at the corresponding pressure **(middle)**. The EDPVR was determined by an exponential fit through the resulting EDPVs **(right)**. Further details are given in the text. Abbreviations as in Figures 1 and 2.

Data were post-processed using Conduct NT-V2.0.1 (CD-Leycom) and a MATLAB platform (The MathWorks, Natick, Massachusetts).

CMR catheterization. CMR ACQUISITION OF VENTRICULAR PRESSURES AND VISUALIZATION OF CATHETERS. After completion of conductance catheter measurements, catheters were replaced under X-ray angiography by 4-F fluid-filled pigtail diagnostic catheters (Cordis, Warren, New Jersey). The balloon catheter for vena cava occlusions was kept unchanged in the inferior vena cava. The pressure catheters were connected to a pressure transducer (Becton-Dickinson, Franklin Lakes, New Jersey) amplified, recorded, and analyzed with Ponemah software (all DSI, St. Paul, Minnesota). Initial pressure recordings were obtained in the catheter laboratory. Thereafter the animals were moved to the CMR laboratory, where steady state hemodynamic conditions were confirmed. In the CMR laboratory, an additional pressure transducer was placed together with the animal within the bore. Radiofrequency pulses induced pressure signal artifacts on this transducer at the beginning of each VEC CMR measurement. These artifacts were used as a trigger signal for synchronizing measured pressures with acquired volume and flow signals (Figs. 2 and 3). Correct catheter position during CMR was confirmed on interactive real-time CMR as previously described (15).

Ventricular volumes and myocardial mass. All CMR studies were performed on a 1.5-T scanner (release 2.6.1, Philips Intera, Best, the Netherlands). Ventricular chamber volumes and myocardial mass were determined from a stack of multislice-multiphase steady-state free-precession cine CMRs covering the entire heart (16). Sequence parameters were: repetition time/echo time 3.4/1.7 ms, slice thickness 6 mm, no gap, in-plane resolution 1.9 × 1.3 mm, 45 phases per cardiac cycle, number of averages 1, sensitivity encoding reduction factor 2. Analysis was performed using View Forum software (Release 6.1, Philips). Biventricular endocardial and epicardial borders were manually traced for computing ventricular volumes and myocardial mass where the septum was accounted left ventricular. Papillary muscles and prominent right ventricular trabeculation were excluded for volume measurements. Stroke volume was calculated as the difference between the diastolic and systolic volumes. Ejection fraction was calculated as the ratio of stroke volume to end-diastolic volumes.

Pulmonary and aortic blood flow. Quantitative blood flow was measured using real-time VEC CMR (17) orthogonal to the dominating flow direction in the pulmonary trunk and the ascending aorta. For the measurements, we corrected for potential phase errors arising from the concomitant magnetic field. Sequence parameters were: repetition time/echo time 23/6.5 ms, matrix 128 × 256, field of view 400 mm, slice thickness 8 mm, encoding velocity 150 cm/s, sensitivity encoding reduction factor 3, half-scan factor 0.6, echo planar imaging factor 41. This resulted in the dynamic scan time of 31 ms for the acquisi-

Table 1. Animal Experiments, Parameters of Cardiac Function by Cine CMR and VEC CMR (Where Indicated)

	At Rest	During Dobutamine Administration
General characteristics		
Body weight (kg)	30.3 ± 6.8	NA
RV muscle mass (g)	27.8 ± 6.3	NA
LV muscle mass (g)	83.9 ± 7.2	NA
Global ventricular pump function		
RV end-diastolic volume (ml)	45.6 ± 9.3	43.6 ± 8.4
RV end-systolic volume (ml)	15.1 ± 4.1	8.6 ± 3.2*
RV stroke volume (ml)	30.6 ± 4.5	35.3 ± 6.3*
RV stroke volume by VEC CMR (ml)	29.6 ± 3.1	34.9 ± 6.5*
LV end-diastolic volume (ml)	46.5 ± 9.6	45.8 ± 7.4
LV end-systolic volume (ml)	16.7 ± 6.3	10.1 ± 4.9*
LV stroke volume (ml)	29.7 ± 4.1	35.7 ± 5.7*
LV stroke volume by VEC CMR (ml)	29.1 ± 4.4	36.4 ± 5.3*
Cardiac output (l/min)	4.0 ± 1.2	6.4 ± 1.4*

*Significant differences ($p < 0.05$) between measurements at rest versus during dobutamine administration. LV = left ventricular; NA = not assessed; RV = right ventricular; VEC CMR = velocity-encoded cine cardiac magnetic resonance.

tion of 1 phase-contrast image, thus an average of 15 acquisitions per heartbeat depending on heart rate. Data analysis was performed with View Forum software. Antegrade and retrograde flows were measured as described elsewhere (18). For validation purposes, we compared left and right ventricular stroke volumes at baseline (without pre-load reduction) as measured with cine CMR and real-time VEC CMR each at rest and during dobutamine administration.

Clinical pilot study. The clinical study was performed in 3 patients with total cavopulmonary connection (Fontan). The patients were referred to our institution for cardiac catheterization and CMR because of decreasing exercise capacity and therefore to determine ventricular systolic and diastolic function and cardiovascular anatomy. After catheterization, the conscious patients were transferred to the CMR laboratory. Measurements were performed during breath-hold at end expiration. All gave informed consent for the study, which was approved by the responsible institutional review committee (reference number 47/04). Except for minor variation in size of the catheters, the conductance and CMR procedures were performed exactly as described in the animal experiments.

Statistical analysis. Agreements between conductance catheter- and CMR-derived β were determined using Bland-Altman tests. Differences between conductance catheter- and CMR-derived parameters as well as measurements at rest and during dobutamine administration were analyzed with a paired Student t test and Bonferroni correction for multiple comparisons where appropriate. Data are expressed as mean ± SD.

RESULTS

Validation study. COMPARISON OF CINE CMR AND VEC CMR STROKE VOLUMES. The data are shown in Table 1. At rest and during dobutamine administration, there was no significant difference between these methods.

CMR versus conductance catheter–derived diastolic compliance. Sequential conductance catheter and CMR measurements were realized at similar hemodynamic conditions, evidenced by the fact that right and left ventricular pressures as well as heart rates were not significantly different between the 2 experimental stages (Table 2). The hemodynamic responses to dobutamine also were similar (Table 2).

The Bland-Altman test showed good agreement between β values determined with the 2 methods at rest and during dobutamine administration (Fig. 5). Importantly, conductance catheter–derived and CMR-derived pressure–volume loops showed parallel changes for measurements of β at rest and during stress (Table 2, Fig. 6). The relative changes of Emax,i were also at similar levels (Table 2).

Response to dobutamine. GLOBAL PUMP FUNCTION (BASED ON CINE CMR). As expected, in response to dobutamine, the right and left ventricle showed a significant increase in stroke volume and cardiac output ($p < 0.01$) (Table 1).

MYOCONTRACTILITY (BASED ON CONDUCTANCE AND CMR CATHETERIZATION). Inotropic stimulation with dobutamine increased Emax,i significantly in both ventricles ($p < 0.01$). The response to dobutamine was more pronounced in the left compared with the right ventricle (Table 2). The noted changes of Emax,i were similar for the conductance catheter and CMR measurements (Table 2).

DIASTOLIC FUNCTION (BASED ON CONDUCTANCE AND CMR CATHETERIZATION). Active early relaxation, as indicated by smaller τ, improved significantly during dobutamine administration in both ventricles ($p < 0.01$) (Table 1). In addition, in all animals and both ventricles, the EDPVR shifted toward the bottom right of the pressure–volume diagram (Fig. 6). There was also a slight but significant decrease of β ($p < 0.05$) (Table 2, Fig. 5). The noted changes were again similar for the conductance catheter and CMR measurements.

Table 2. Animal Experiments, Parameters of Cardiac Function by CMR and Conductance Catheter

	CMR		Conductance Catheter	
	At Rest	During Dobutamine Administration	At Rest	During Dobutamine Administration
Hemodynamic data				
Heart rate	93 ± 16	133 ± 12*	89 ± 14	141 ± 14†
RV ESP/EDP pressures (mm Hg)	25.2 ± 7.7/5.1 ± 2.4	39.5 ± 5.7*/4.6 ± 1.4	24.2 ± 6.8/4.8 ± 2.8	41.2 ± 6.7†/4.4 ± 1.7
LV ESP/EDP pressures (mm Hg)	66.5 ± 10.1/4.6 ± 2.2	109.2 ± 11.9*/4.2 ± 1.5	63.4 ± 10.1/4.4 ± 2.1	103.2 ± 13.1†/4.1 ± 2.2
Myocardial contractility				
RV Emax,i (mm Hg/ml/100 g MM)	3.1 ± 1.9	5.2 ± 3.1*	3.6 ± 0.6	5.7 ± 1.5†
LV Emax,i (mm Hg/ml/100 g MM)	1.6 ± 0.6	3.3 ± 1.6*	1.8 ± 0.7	3.6 ± 1.1†
Diastolic relaxation				
RV τ (ms)	36.1 ± 9.2	27.2 ± 8.1*	39.4 ± 6.1	31.6 ± 5.4†
LV τ (ms)	31.8 ± 8.2	25.5 ± 7.3*	33.5 ± 6.6	22.9 ± 5.6†
Diastolic compliance				
RV β (1/ml)	0.024 ± 0.007	0.011 ± 0.008*	0.021 ± 0.005	0.010 ± 0.008†
RV β,i (1/ml/100 ml EDV)	0.011 ± 0.004	0.004 ± 0.002*	0.010 ± 0.002	0.007 ± 0.003†
LV β (1/ml)	0.027 ± 0.004	0.016 ± 0.006*	0.023 ± 0.009	0.015 ± 0.007†
LV β,i (1/ml/100 ml EDV)	0.012 ± 0.002	0.007 ± 0.003*	0.010 ± 0.003	0.004 ± 0.003†

*Significant differences ($p < 0.05$) between measurements at rest versus dobutamine for magnetic resonance. †Significant differences ($p < 0.05$) between measurements at rest versus dobutamine for conductance catheter measurements.
β = stiffness constant; β,i = stiffness constant indexed to 100 ml end-diastolic volume; EDP = end-diastolic pressure; EDV = end-diastolic volume; Emax,i = slope of the end-systolic pressure volume relation indexed to 100 g muscle mass; ESP = end-systolic pressure; MM = muscle mass; τ = parameter of early diastolic relaxation; other abbreviations as in Table 1.

Clinical experiments. Oxygen saturation was above 95%, also unaltered during dobutamine administration. All Fontan circuits were free from obstructions. Concordantly during dobutamine administration there was a decrease of end-diastolic and -systolic volumes (Table 3). Contractility, stroke

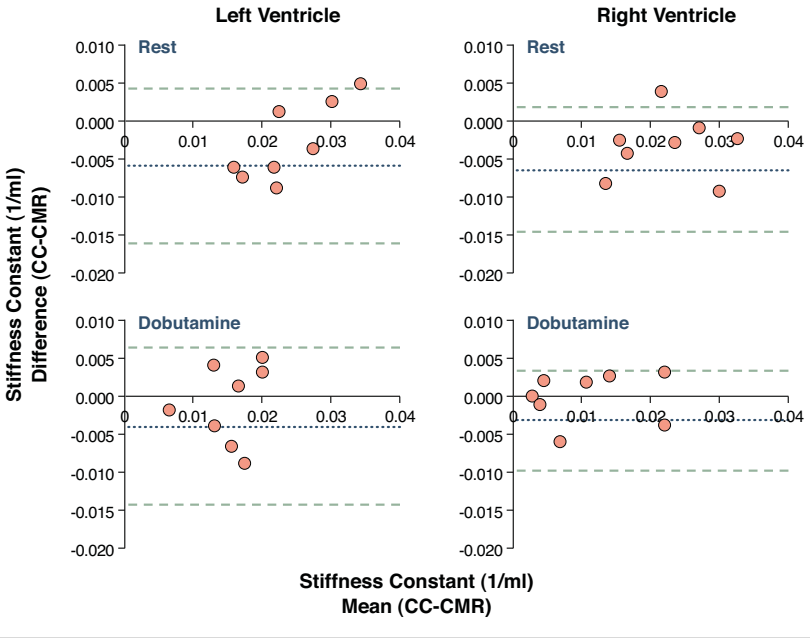

Figure 5. Comparison of Ventricular Stiffness Constant Measured by CC and by CMR

Bland-Altman plots show the difference between the results from conductance catheter (CC) and CMR measurements in 8 pigs for left and right ventricular stiffness constant **(left, right)**. Measurements were performed at rest and during dobutamine and are shown in separate plots. In all plots there is a negative bias, which indicates a slight but consistent overestimation by CMR in both the left and the right ventricle. Abbreviations as in Figure 1.

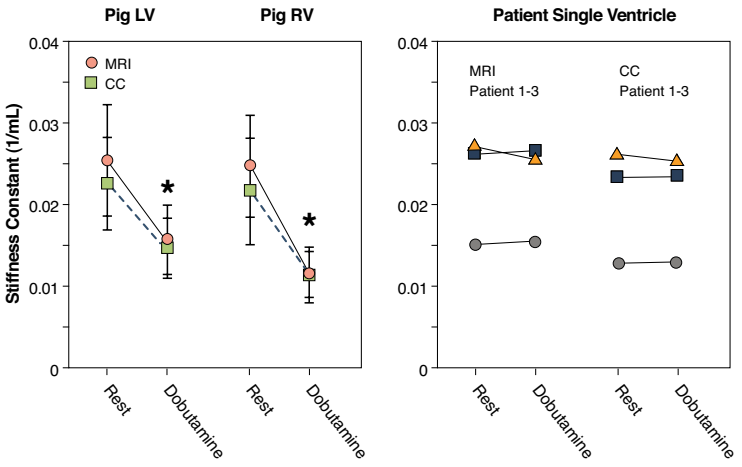

Figure 6. Changes in Stiffness Constant During Dobutamine Administration

Ventricular stiffness constants as measured with CMR and CC techniques in the pig left and right ventricle and in 3 patients with a single ventricle. There are no statistically significant differences between the CC and CMR measurements. In addition, this figure shows parallel decreases in the stiffness constant in CMR and CC measurements during dobutamine administration in pigs but no significant changes in Fontan patients. A value of $p < 0.05$ was considered significant. Abbreviations as in Figure 5.

volumes, and heart rate increased slightly, resulting in elevated cardiac outputs (Table 3). Active early relaxation was slightly enhanced. In contrast, the EDPVR shifted toward the left in the pressure–volume diagram and β remained nearly unchanged (Table 3, Figs. 6 and 7). Similar observations were made with conductance catheter and CMR techniques (Fig. 6).

Table 3. Clinical Study Data for Patients #1 to #3

	At Rest	During Dobutamine Administration
Global parameters		
Age (yrs)	19 ± 0.8	NA
Age at Fontan operation (yrs)	3 ± 0	NA
Body surface index (kg/m^2)	1.3 ± 0.1	NA
Heart rate (beats/min)	81 ± 3.3	113 ± 5
Ventricular volumes		
End-diastolic volume (ml/BSA)	97 ± 6.5	92.3 ± 7
End-systolic volume (ml/BSA)	53.7 ± 5	46.7 ± 4
Stroke volume (ml/BSA)	43.3 ± 1.9	45.7 ± 3.3
Ejection fraction (%)	44.8 ± 1.7	49.5 ± 1.2
Blood flow volumes		
Aorta (l/min)	3.7 ± 0.5	5.1 ± 0.5
Ventricular pressures		
End-diastolic pressure (mm Hg)	5.1 ± 0.4	5.8 ± 0.4
End-systolic pressure (mm Hg)	90.3 ± 4.9	103.7 ± 5.4
Contractility		
Emax,i (mm Hg/ml/100 g muscle mass)	3.5 ± 0.4	4.4 ± 0.4
Diastolic compliance and relaxation		
β (1/ml) × 100	2.3 ± 0.6	2.3 ± 0.8
β,i (1/ml/100 ml EDV) × 100	1.4 ± 0.3	1.4 ± 0.3
τ (ms)	36 ± 0.8	29.3 ± 1.2

Values are mean ± SD. All data are based on measurements during CMR. Individual data from each patient for conductance catheter-derived and CMR-derived stiffness constant are shown in Figure 7.
BSA = body surface area; other abbreviations as in Table 2.

DISCUSSION

We developed and validated a novel method for estimating the EDPVR, an index of ventricular chamber stiffness, by combining invasive pressure measurements with noninvasive real-time CMR volume and flow data. Our results indicate that the proposed method is suited to determine left and right ventricular chamber stiffness in conjunction with parameters of contractility and global pump function.

Technical consideration. The ESPVR and EDPVR are widely used in physiological studies because they reflect intrinsic systolic and diastolic myocardial function in a relatively load-independent fashion. Clinical application is still limited, mainly because of technical difficulties in performing the required measurements. The proposed CMR method might potentially expand clinical application because it is technically straightforward, and once the small and user-friendly catheters are in place, a complete set of right and left ventricular pressure–volume acquisitions can be obtained in <10 min.

Ideally, ESPVR and the EDPVR are determined from a family of pressure–volume loops during transient pre-load reduction (9,10). Previously, methods were introduced to estimate the ESPVR by single-

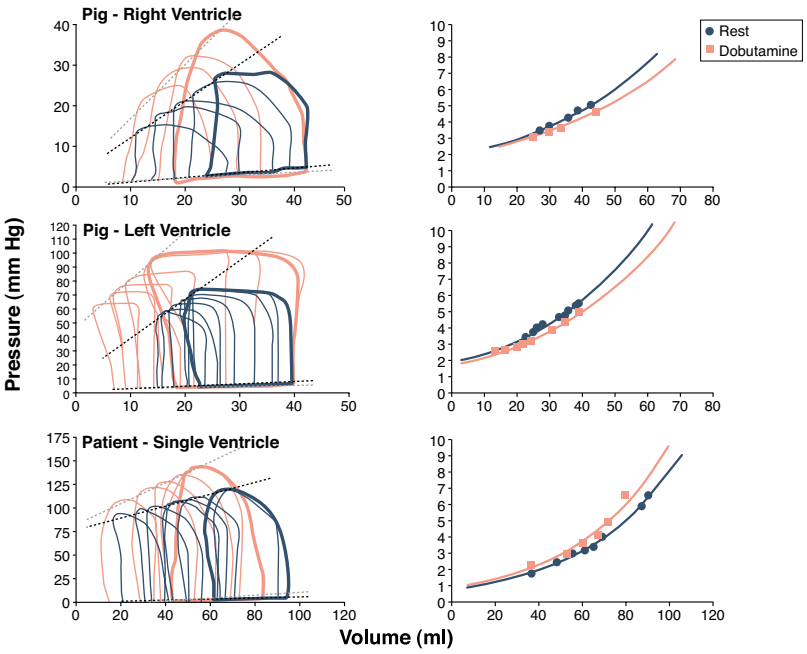

Figure 7. Ventricular Stiffness in the Healthy Animal Heart and in Fontan Patients

Representative CMR-derived pressure–volume loops of a pig right and left ventricle and a patient with a single ventricle. The end-systolic pressure–volume relation (ESPVR) and end-diastolic pressure–volume relation (EDPVR) at rest and during dobutamine administration are shown **(left, dashed lines)**. The EDPVRs are shown more detailed **(right)**. Note the left shift of the relation in the patient as opposed to the right-bottom shift in the pig's right and left ventricle during dobutamine administration. Abbreviations as in Figure 1.

beat approaches (7,8,13,19). However, similar simplified approaches to estimate the EDPVR are complicated by its inherent nonlinearity. Therefore, load interventions, which are commonly performed by balloon occlusion of the vena cava, are needed for determining profiles of ventricular chamber stiffness.

The conductance catheterization is an established method for measuring ventricular pressure–volume relations in animal experiments and human studies. However, by theory it requires a symmetrically shaped ventricle, and derived volumes need calibration with volumes obtained by a valid reference method, such as CMR (20). Consequently, conductance measurements in the nonsymmetrically shaped right ventricle or in a variety of congenitally malformed hearts can be problematic. Particularly these patients often need a differential analysis of ventricular systolic and diastolic function to determine optimal treatments.

To date, CMR is considered the gold standard in terms of accuracy and reproducibility for quantification of ventricular volumes (4,5). As mentioned, this measurement accuracy is crucial for the assessment of pressure–volume relations, particularly in asymmetrically shaped ventricles. Measurement errors by calibrating issues or by geometric assumptions are avoided (14,21). Similar to the conductance catheter, the CMR method proposed in this study requires invasive measurement of pressures. The fluid-filled CMR catheters used were, however, substantially smaller in size (4-F vs. 7-F) and easily positionable. To avoid susceptibility artifacts or radiofrequency pulse-induced heating during CMR, the application of metallic high-fidelity pressure-tipped catheters was excluded, and consequently materials without metallic components were used (15). A potential down side of fluid-filled catheters is the attenuation of pressure amplitudes. To minimize this effect, we limited the total length of the catheter and the connecting pressure line to <1 m.

In the current study, we determined the ESPVR using a single-beat approach as previously reported (7,8,13,19). This approach implies that ventricular volumes are measured by cine CMR over several beats and are synchronized with pressures averaged for the same time period. To minimize beat-to-beat variability, keep the hemodynamic condition and state of ventilation at identical levels during data acquisition.

Physiologic aspects. In the animal study, during dobutamine administration, diastolic function improved by faster early relaxation in conjunction with a slight bottom-right shift of the EDPVR. Similar to observations in previous studies (20,22), we also

noted a decrease of β. In contrast, in the patients, the EDPVR shifted during dobutamine administration toward the upper left in the pressure–volume diagram. Early relaxation improved slightly, and β did not change substantially.

Several reasons can account for the noted abnormal diastolic function in Fontan patients. The single ventricle, no matter of left/right type, is mostly of abnormal geometric shape with a direct impact on the mechanical properties of the ventricle and thus on systolic and diastolic function (12). Moreover, a recent pathohistological study showed abnormal myoarchitecture of the connective tissue matrix (23). During infancy these ventricles are exposed to prolonged cyanosis and volume load, which may induce fibrosis and thus have an impact on diastolic stiffness (24).

Accordance exists that the EDPVR reflects chamber capacity and compliance. Similar to the ESPVR, this relation is influenced by ventricular configuration, including size, and heart rate. Therefore, the impact of volume and heart rate changes during dobutamine administration must be considered when interpreting these data. The tendency toward a smaller β in the animal study and an invariable β in the patients was, however, also noted when β was indexed to ventricular chamber size (Tables 2 and 3).

In our study, parameters of contractility and chamber stiffness were measured with conductance catheter and CMR techniques nonsimultaneously. As mentioned earlier, alteration in volume load and heart rate, which can be induced among other factors by prolonged sedation, may have an impact on the ESPVR and EDPVR. We were able to keep baseline hemodynamic parameters, including heart rate, stable with changes of $<$10% between the sequential measurements (Table 2). We recommend measuring the EDPVR with the proposed CMR catheterization technique at heart rates of no more than 150 beats/min. This is for purely physiological reasons and for allowing reasonable temporal resolution in the real-time CMR flow measurements. The development of faster real-time CMR applications should be subject to future research.

Normalization of contractile and stiffness indexes may be required when comparing different study populations. Concerning the diastolic β, Burkhoff et al. (9) suggested the use of a dimensionless index by multiplying β by the myocardial wall volume, which can be directly obtained from the acquired cine CMR scans. The variability of wall volume measurements, particularly for the right ventricle, is known to be substantial (25). As an alternative, β might be normalized to chamber volume. This important issue must be systematically investigated in future research.

Study limitations. The CMR and conductance catheter measurements cannot be performed simultaneously. For comparison of measured data, we aimed for keeping the animals' physiological conditions, such as heart rate and blood pressure constant. Care must be taken when comparing physical exercise with dobutamine stress (26). Therefore, it would be inappropriate to directly translate our findings regarding chamber stiffness during dobutamine administration to exercise conditions. Some technical limitations should be mentioned. In the CMR setting, we measured ventricular pressures with fluid-filled catheters to avoid metallic components, in contrast with the high-fidelity, solid-state sensors incorporated in the conductance catheter. A fluid-filled catheter manometer system acts as a low-pass filter, thus high-frequency components are attenuated. However, by using relatively stiff and short catheters and carefully removing trapped air bubbles, adequate recordings of cardiac and arterial pressure signals can be obtained and the impact on derived indexes is expected to be very limited (27). For indexes that require high-frequency components, such as relaxation time constants, CMR-compatible pressure catheters or sophisticated signal processing may need to be considered (28,29). VEC CMR measurements are susceptible to several potential sources of error, which include turbulent flow and moving valve planes. The CMR method was introduced to the clinical scenario in a small, well-controlled pilot study. Future studies must include a much larger number of patients.

CONCLUSIONS

This work presents an CMR catheterization method for the assessment of diastolic and systolic pressure–volume relation in the left and right ventricle. The applied method combines cine CMR ventricular volumes, real-time VEC CMR blood flow, and invasive ventricular pressure measurements. Our results indicate that the proposed CMR method provides, in addition to parameters of systolic contractile and global pump function, accurate load-independent indexes of biventricular diastolic function. The proposed CMR method might potentially expand the application of pressure–volume relation in the clinical con-

text. Because ventricular volumes are measured by CMR without geometric assumptions, the technique might also be suitable for assessment of right ventricular disorders or congenitally malformed hearts.

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